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EXAMINER
NGUYEN, DAVE TRONG

ART UNIT	PAPER NUMBER
1632	

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15

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/811,323	German
Examiner	**Art Unit**
Dave Nguyen	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 24, 2003*.

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *18, 19, and 21-60* is/are pending in the application.

4a) Of the above, claim(s) *26, 28, 34-45, and 47-51* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *18, 19, 21-25, 27, 29-33, 46, and 52-60* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Mar 16, 2001* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *, 12, 1*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Claim 20 has been canceled, claims 52-60 have been added by applicant in the amendment dated March 13, 2003.

Claim 51 has been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claimed invention. A complete response to the final rejection must include cancellation of non-elected claims or other appropriate action (37 CFR 1.144) MPEP 821.01.

Claims 26, 28, 34-45, 47-50 readable on non-elected species have been withdrawn by the examiner.

Claims 18-25, 27, 29-33 and 46 are pending for examination.

For the purpose of a complete examination of all of the outstanding issues embraced by the generic claim insofar as it does not institute an undue burden on the examiner, species of plasma protein, *e.g.,* insulin, as recited in claim 46 has been rejoined to the species examination.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18-25, 27, 29-33, 46, and 52-60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, because the specification, while being enabling for

A method of delivering a non-therapeutic secreted protein into the bloodstream of a mammalian subject, the method comprising:

Introducing into the gastrointestinal tract of a mammalian subject by an oral administration of a construct comprising a nucleic acid molecule encoding a secreted protein and a promoter operably linked to the nucleic acid molecule, wherein said construct is not packaged in a viral particle, said introducing resulting in introduction of the construct into an intestinal epithelial cell and secretion of the protein from the cell and into the bloodstream of the subject;

A method of inducing an immune response to a secreted protein in the bloodstream of a mammalian subject, the method comprising:

Introducing into the gastrointestinal tract of a mammalian subject by an oral administration of a construct comprising a nucleic acid molecule encoding a secreted protein antigen and a promoter operably linked to the nucleic acid molecule, wherein said construct is not packaged in a viral particle, said introducing resulting in introduction of the construct into an intestinal epithelial cell and secretion of the protein from the cell and into the bloodstream of the subject, thereby inducing the immune response in the mammalian subject;

A method for reducing blood glucose levels in a hyperglycermic mammal, the method comprising

introducing into the gastrointestinal tract of a mammalian subject by an oral administration of a construct comprising a controlled release formulation or polymeric capsule that encapsulates a nucleic acid molecule encoding a secreted insulin protein, wherein said construct is not packaged in a viral particle, said introducing resulting in introduction of the construct into an intestinal epithelial cell and secretion of the insulin protein from the cell and into the bloodstream of the subject in an amount effective to reduce blood glucose levels;

A method for reducing blood glucose levels in a hyperglycermic mammal, the method comprising

introducing directly into the gastrointestinal tract of a mammalian subject by an oral administration of a construct comprising a nucleic acid molecule encoding a secreted insulin protein, wherein said construct is not packaged in a viral particle, said introducing resulting in introduction of the construct into an intestinal epithelial cell and secretion of the insulin protein from the cell and into the bloodstream of the subject in an amount effective to reduce blood glucose levels;

does not reasonably provide enablement for the claimed invention as broadly claimed presently. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

NATURE OF INVENTION, GUIDANCE AND WORKING EXAMPLES

The application indicates that the present invention provides methods of treatment using gene therapy, more specifically gene therapy by expression of a DNA of interest in the GI tract (page 5, lines 7-25, and pages 6-9), and that the DNA of interest preferably encodes insulin, a growth hormone, clotting factor VIII, intrinsic factor, erythropoietin, factor IX, and all other blood factors (page 16 bridging page 19). Thus, it appears that the only disclosed method of use for the gene delivery through the bloodstream and expression of a polypeptide in the bloodstream is to have a therapeutic effect. Table 2 on pages 24-25 lists an enormous number of diseases including obesity, bone disease, allergic rhinitis, asthma, Addison's disease, spontaneous infertility, Vitiligo, arthritis, Polymyositis, Enzyme deficiency, cancer, and cardiovascular diseases that are compassed by the claimed gene therapy methods and pharmaceutical compositions. Note also that the claims also embrace the use of a DNA construct encoding a non-secretory protein and yet claiming that the expressed non-secretory protein, *e.g.,* CFTR, can be transported extracellulary into the bloodstream. The application demonstrates that a direct injection of plasmid vectors expressing human insulin polypeptides into the GI tract of rats suffering from diabetes reduces blood glucose levels in treated rats (Example 4, Figure 7). Furthermore, Example 5 of the

application provides data demonstrating that an injection of plasmid vectors expressing human growth hormones (hGH) via a catheter into the duodenum of the GI tract in rats allows expression of hGH in the bloodstream (Figure 11), wherein there is no therapeutic effect shown as the result of the hGH expression. However, the specification does not teach or provide sufficient guidance for one skilled in the art to reasonably extrapolate, without undue experimentation, from the efficacy of plasmid vectors expressing human insulin in suppressing the diabetic syndrome in streptozotocin-treated rats to methods of treating all other diseases or disorders in any or all mammals, wherein DNA encoding any and all other therapeutic proteins and/or wherein any other administration route is employed.

THE STATE OF THE PRIOR ART, THE LACK OF A REASONABLE CORRELATION BETWEEN APPLICANT'S GUIDANCE AND WORKING EXAMPLES TO APPLICANT'S BREADTH OF THE PRESENTLY PENDING CLAIMS.

Major considerations for any gene transfer or gene therapy protocol involve issues that include:

1/ The effect of an immune response against a gene therapy DNA before a therapeutic effect is generated;

2/ The type of vector and amount of DNA constructs to be administered;

3/ The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site; and

4/ What amount is considered to be therapeutically effective for a gene therapy method (Coghlan, New Scientist, Vol. 148, pp. 14 and 15, 1995; Anderson, Nature, Vol. 392, 25-30, April 1998; and Gunzburg *et al.*, Vol. 1, No. 9, pages 410-417, 1995).

More specifically as to the unpredictability of gene therapy at the time the invention was made, Anderson summarized the state of the art before 1998, and teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (page 30, column 1, last paragraph). Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is

that we still lack a basis understanding of how vectors should be constructed, what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph).

With regard to the use of liposome for administration *in vivo*, Ledley (Human Gene Ther. (1995) 6:1129-1144) teaches that "Many formulations that are effective *in vitro* fail to function *in vivo*...It is, in fact, not surprising that in vitro studies with gene delivery systems have not been predictive of in vivo functionality" (p. 1138, col. 1). Ledley also discloses several important biological constrains for *in vivo* nonviral gene delivery such as the bioavailability of the gene to the target cell, the physical chemistry of the cell surface, the rapid elimination of DNA from intravascular or interstitial compartments after administration, effects of the physicochemical properties of the administered complex in vivo, and the molecular biology of specific receptors and intracellular trafficking events (pp. 1138-39). More specifically, Ledley states that "it is unlikely that any one method for gene transfer will prove to be effective in every organ. Rather, various formulations will need to be developed that can be used to deliver DNA to specific targets based on the biological properties of that target" (p. 1139, col. 1).

Also see Abendroth, abstract, EMBASE, AN 96126219, 1996, and Ponder, abstract cited from MEDLINE, AN 200103902 as to the unpredictability of human gene therapy at the time the invention was made and even in 1999. Verma *et al.* (Nature, Vol. 389, 18, September 1997) also states that "the Achilles heel of gene therapy is gene delivery", that "thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression", that gene delivery methods using non-viral vectors "suffer from poor efficiency of delivery and transient expression of the gene", and that "although there are reagents that increase the efficiency of delivery, transient expression of the transgene is a conceptual hurdle that needs to be addresses" (page 239, column 3, first paragraph). Furthermore, Verma *et al.* indicate that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2).

Coghlan (New Scientist, November 1995) states that problems with gene therapy involve gene

targeting and the number of genes reaching the target cells-estimated by some researchers to be about 1%. Coghlan discloses that even those genes, which reach their destination work inefficiently, producing too little protein for too short a time period to benefit the patient. Neither the application nor the incorporated references provide evidence showing that any and/or all pharmaceutical compositions other than the composition of an insulin encoded DNA would generate a therapeutic effect when employed in any of the disclosed gene therapy method. The evidences obtained from the working examples are not reasonably predictable and correlated to a therapeutic effect in any or all subjects using a genus of claimed pharmaceutical compositions as claimed. In fact, Ledley (Human Gene Ther. (1995) 6:1129-1144) teaches:

"it is unlikely that any one method for gene transfer will prove to be effective in every organ. Rather, various formulations will need to be developed that can be used to deliver DNA to specific targets based on the biological properties of that target" (p. 1139, col. 1).

Furthermore, Doerfler *et al.* (Gene, 157/1-2, pp. 241-245, 1995, abstract) teach that when naked DNA is feed orally in mice, "a small amount of this DNA transiently survives the digestive regime of the animals ' GI tract, although in a heavily fragmented form", and that "a minute proportion of the fed M13mp18 DNA can be retrieved from the bloodstream of mice between 2 and 8 h after feeding, mainly associated with the leukocyte population" (abstract).

Thus, it is not apparent how one skilled in the art determines, without undue experimentation, which of the genetic constructs or pharmaceutical compositions other than the insulin encoded DNA, and/or antigen encoding DNA for the purpose of inducing an immune response in the bloodstream of a mammal as disclosed in the as-filed application, would produce a therapeutic effect, particularly in view of the doubts expressed in the art of record at the time the invention was made.

While the specification demonstrates expressions of insulin pancreas of rats whereby glucose reduction was generated in the treated rats, it is not apparent whether such particular methods employing specific DNA constructs are reasonably extrapolated to any therapeutic effect by using any administration of any other protein encoded DNA in any human patient within the context of applicant's teaching (gene

therapy see the entire specification), nor is it apparent how one skilled in the art extrapolates expression of hGH or insulin in rats to gene therapy methods using genetic constructs expressing therapeutic genes such as clotting factor VIII, erythropoietin, interferon-alpha 2b, interferon-alpha 2a, interleukin-2, interferon-alpha, adenosine deaminase, insulin-like growth factor-1, platelet-derived growth factor, and epidermal growth factor in a human patient within the context of intended therapeutic application of the gene therapy method as claimed. Note that a simple expression of growth factor IX in the bloodstream in mice, a simple expression of human growth hormone in rats, and an increase of blood cells (hematocrits) as a result of expression of human EPO in rats, all of which models employ direct retroductal injection of naked plasmid encoding respective proteins, are not the same as claiming an oral route of introduction of any DNA encoding any therapeutic into the GI tract in any mammal including a human patient so as to provide a therapeutically relevant effect, nor is it the same as a therapeutic effect within the context of the teachings provided by the as-filed specification. Neither the working murine or rat models can be considered as a general observed phenomenon so as to reasonably extrapolated to any human gene therapy to treat any human disease or disorder as presently claimed, particularly on the basis of applicant's disclosure and given the doubts expressed in the art of record and the sufficient reasons set forth in the stated rejection.

Thus, in view of the lack of guidance regarding the subject matter of the claims within the context of human gene therapy of using any therapeutic DNA for treatment of any disease or disorder through hepatic route of DNA delivery, state of the art and the unpredictability of the art, as set forth by the evidence presented above, undue experimentation would be required by one of ordinary skill to practice the invention as claimed.

With respect to the breadth of the base claim that embrace the making and use of a non-secretory protein encoded DNA sequence that must exhibit the ability to be transported extraceullarly into the bloodstream from a transfected intestinal epithelial cell, the as-filed specification does not provide any guidance as to how such contemplated property can be accomplished with a DNA encoding a non-secretory protein. As such, the as-filed specification only provides a reasonable enablement for claims

readable the making of a DNA construct encoding a secretory protein, which exhibits the ability to be transported extracellularly into the bloodstream due the presence of a signal sequence in the coding region of the protein.

Note also that the specification fails to teach any specific targeting techniques, fails to provide sufficient guidance and/or factual evidence to demonstrate any vector targeting other than *in vivo* direct injection of a DNA construct expressing an insulin gene product so as to generate a therapeutic effect, and fails to direct the skilled artisan to any teachings of targeting strategies and of using vector constructs other than injection of the insulin expressing constructs into the GI tract of a subject which would allow one of skill in the art to practice the full scope of the claimed invention without undue experimentation, particularly in view of the doubts expressed in the art of record.

Applicant's response (pages 6-13) has been considered by the examiner but is not found persuasive in view of the reasons set forth in the stated rejection and the following reasons:

In response to applicant' s assertion (the response, pages 6, 7) that applicant's claims are not directed to treatment gene therapy methods for correcting any disease but rather a method of delivering a gene product of interest into the bloodstream *in vivo,* and that applicants have demonstrated that the scope of enablement bears a reasonable correlation to the scope of the claims, the comments are persuasive as to the method claims because one of skill in the art would recognize that there is an apparent utility and reasonable predictability of using the claimed gene transfer method for delivering DNA encoding antigenic peptides, or viral protein products into the bloodstream of a subject so as to generate an elicitation of an immune response to the delivered protein product in the bloodstream. However, the claimed gene therapy methods as presently claimed in the form of the delivery methods encompass an enormous number of therapeutic DNA, and because of the reasons set forth in the above stated rejection and because of the unpredictability of gene therapy as a whole, one skilled in the art would have to engage an undue experimentation to determine as to which of the pharmaceutical compositions disclosed in the specification other than the pharmaceutical composition of the insulin encoded DNA would operate as the "pharmaceutical". As such and in view of the doubts expressed in

the art of record, one of skilled in the art would not have been able to reasonably extrapolate from the a reduction of blood glucose levels in a hyperglycermic rat to a therapeutic effect of an oral gene therapy method of using a growth hormone encoded non-viral construct, let alone of other gene therapy methods as broadly embraced by the presently pending claims.

Applicant further asserts that since none of the cited art employs applicant's gene therapy methods, and that the cited arts are not relevant to the patentability of the claimed invention under 35 USC 112, first paragraph. In response, the examiner maintains that the cited prior art clearly indicates that for any gene therapy protocol to be successful, a number of factors must be considered: these factors are:

1/ The effect of an immune response against a gene therapy DNA before a therapeutic effect is generated;

2/ The type of vector and amount of DNA constructs to be administered;

3/ The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site; and

4/ What amount is considered to be therapeutically effective for a gene therapy method (Coghlan, New Scientist, Vol. 148, pp. 14 and 15, 1995; Anderson, Nature, Vol. 392, 25-30, April 1998; and Gunzburg *et al.*, Vol. 1, No. 9, pages 410-417, 1995).

Given that applicant's gene therapy method as claimed in the form of the non-viral delivery methods employ a DNA construct and involves the very same issues and/or factors as set forth in the cited art, the cited art remain deemed relevant to the outstanding issues under 35 USC 112, first paragraph **regardless of whether an oral route of administration is employed**. Note that an oral route of administration not only does not change the obstacles in overcoming the factors as set forth in the cited prior art and above but also further complicates a successful outcome an gene therapy method, particularly give the problems associated with stomach acidity and enzymatic digestions. Thus, when all of the *Wands* factors and the evidence including specific technical reasons are analyzed as a whole, it is apparent that the examiner has met the burden to establish a reasonable basis to question the

enablement provided by the full scope of the claimed invention, *e.g.*, the gene therapy vector systems and/or pharmaceutical compositions.

Applicant's response with respect to the citation of the Coghlan reference has been considered but is not found persuasive because to the extent that an in vivo administration of any genetic construct including those of applicant's constructs results only in an transient expression of a protein, and that such transient gene expression is not the same as a therapeutic effect, as evidenced by other cited references, the Coghlan reference does reflect the state of the art of the gene therapy, and applicant's invention is an gene therapy *per se* wherein an oral administration of a non-viral vector encoding any therapeutic gene product is employed.

Applicant further attempts to equate a simple *jn vivo* expression of human growth hormone in rats (page 8) to a successful gene therapy outcome. However, Example 5 of the application provides data demonstrating that an injection of plasmid vectors expressing human growth hormones (hGH) via a catheter into the duodenum of the GI tract in rats allows expression of hGH in the bloodstream (Figure 11), wherein there is no therapeutic effect shown as the result of the hGH. As such and given that the claimed invention embraces any gene therapy of treating any disease or disorder by an oral administration of any non-viral vector expressing a therapeutic product in the bloodstream of any mammal, it is apparent that one single showing of a reduction of blood glucose levels in a hyperglycermic rat can not be reasonably extrapolated to a successful outcome of any gene therapy protocol as broadly claimed by applicants, particularly in view of the doubts expressed in the art of record. The examiner again respectfully submit that applicant attempts to claim that applicant's claimed oral gene therapy drawn to any gene therapy protocol of treating any disorder or disease by orally administering any non-viral vector construct expressing any therapeutic protein, and as such, the totality of the art of record does provide sufficient evidence to drawn a reasonable conclusion that at the time the invention was made, gene therapy is not a routine matter, and a successful outcome of one particular gene therapy protocol does not necessarily correlate to that of another therapeutic DNA employed gene therapy protocol.

Applicant continues to assert (page 8) that targeting is not required by the claimed gene therapy methods. However and given the fact that applicant 's claimed oral gene therapy is not simply for treating a disorder in the GI tract but rather embraces a treatment of any disorder or disease at any distant site, targeting is required and embraced by the claimed gene therapy methods, even though the word "targeting" is not explicitly recited in the claims. Notwithstanding the problem of gene targeting associated with the lack of the predictability of gene therapy, the examiner respectfully submit that Ledley does indicate that "Many formulations that are effective *in vitro* fail to function *in vivo*...It is, in fact, not surprising that in vitro studies with gene delivery systems have not been predictive of in vivo functionality" (p. 1138, col. 1). Ledley also discloses several important biological constrains for *in vivo* nonviral gene delivery such as the bioavailability of the gene to the target cell, the physical chemistry of the cell surface, the rapid elimination of DNA from intravascular or interstitial compartments after administration, effects of the physicochemical properties of the administered complex in vivo, and the molecular biology of specific receptors and intracellular trafficking events (pp. 1138-39). More specifically, Ledley states that "it is unlikely that any one method for gene transfer will prove to be effective in every organ. Rather, various formulations will need to be developed that can be used to deliver DNA to specific targets based on the biological properties of that target" (p. 1139, col. 1). As such, applicant's response is simply an opinion and does not provide any evidentiary support to show that applicant is fully enabling for the claimed invention as broadly claimed. As such, the Ledley reference is relevant to **a person with a relatively high skill in the art of gene therapy**, particularly in view of the totality of the art of records and the reasons set forth above. Note that statements indicating promises in gene therapy protocols (applicant's responses, page 9) do not indicate *per se* that at the time the invention was made, undue experimentation is not required to practice the claimed invention as broadly claimed. Note also that the fact that the Gunzburg reference is mainly focused on the lack of predictability of gene therapy of using a viral vector does not necessarily mean that non-viral vector gene therapy is reasonably predictive at the time the invention was made. Insofar as the immune response is a major factor in destroying exogenous therapeutic DNA employed in a gene therapy protocol, the Gunzburg reference is relevant to the claimed

invention, and to the extent that numerous references do teach and suggest numerous problems associated with gene therapy protocols including those of using a non-viral vector construct, the rejection remains proper under 35 USC 112, first paragraph. Further as well stated by the totality of the cited art, the fact that non-viral vectors do not provide high level of gene expression as that of a viral vectors when introduced *in vivo,* the fact that numerous gene therapy protocols employing viral vectors provide disappointing results, a person skill in the art of gene therapy in light of the totality of the cited art would not have reasonably conclude that the result of any a non-viral gene therapy protocol is anything different than that of a viral vector employed gene therapy protocol. Applicant's brief response with respect to Verma again is not deemed sufficient to remove the objective doubts expressed by Verma as an exemplified art of record. Note that Verma clearly indicates that that "the Achilles heel of gene therapy is gene delivery", that "thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression", that gene delivery methods using non-viral vectors "suffer from poor efficiency of delivery and transient expression of the gene", and that "although there are reagents that increase the efficiency of delivery, transient expression of the transgene is a conceptual hurdle that needs to be addresses" (page 239, column 3, first paragraph). Furthermore, Verma *et al.* indicate that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2). As such, the **efficiency of delivery, transient expression of the transgene by an *in vivo* administration of a non-viral vector so as to produce a gene therapy successfully therapeutic outcome remain relevant to that of the claimed invention.** As such, a showing of a simple production and enhancement of blood glucose levels in a hyperglycemic rat can not be reasonably extrapolated to a successful outcome of any gene therapy protocol as broadly claimed by applicants, particularly in view of the doubts expressed in the art of record.

In response to applicant' s assertion (the response, page 11) that the Doerfler reference does support applicant's argument that oral delivery of DNA into the bloodstream is enabled, the comments are

not persuasive because it is not apparent as to how the orally delivered DNA once degraded into random fragment in the blood expresses an intended encoded DNA, nor it is apparent as to how the presence of random fragment of degraded DNA in the bloodstream is reasonably correlated to a genus of pharmaceutical compositions as claimed.

Applicant's response with respect tot the Anderson reference is essentially the same as to applied to other cited references, and thus, the examiner maintains that the Anderson reference remain relevant to the state of the art and does provide evidentiary support to indicate that gene therapy is not routine experimentation. More specifically, Anderson teaches that results in one particular animal model have not always reflected what happens in another animal model (page 28, column 1, first paragraph), that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (page 30, column 1, last paragraph). Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack a basis understanding of how vectors should be constructed, what regulatory sequences are appropriated for which cell types. These kinds of statements along with that of other cited references do not appear in any way to suggest that applicant's claimed invention as broadly claimed for treatment of any disease or disorder when reasonably read in light of the specification is reasonably enabling at the time the invention was made.

The Roth Declaration dated March 27, 200 coupled with Applicant's comments regarding the Roth Declaration have been considered fully by the examiner, and are found persuasive as to applicant's assertion that direct injection of a non-viral DNA into the GI tract for a simple gene expression can be achieved successfully either by an intraluminal route of administration or by an oral administration using the gavage. However, the Declaration does not provide any evidentiary support to show that applicant 's claimed invention is reasonably enabling in its full breadth at the time of filing, even thought applicant is not required to exemplify every possible species as embraced by the claimed invention. However, the court in Enzo 188

F.3d at 1374, 52 USPQ2d at 1138 states:

> It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. In re Vaeck, 947 F.2d 488, 496 & n.23. 30 USPQ2d 1438, 1445 & n23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specifications provide no more than a "plan" or "invitation" for those of skill in the art to experiment...; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d...[1557], 1562, 27 USPQ2d...[1510], 1514. [footnote omitted].

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in—
>
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
>
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claims 18-25, 27, 30-33, 46, and 52-60 are rejected under 35 U.S.C. 102(e) as being anticipated by Mathiowitz *et al.* (US Pat No. 6,248,720 B1).

The claims are readable on a method of orally delivering a secreted protein antigen or an insulin protein in the bloodstream of a mammalian subject, the method comprising:

Introducing into the gastrointestinal tract of a mammalian subject by an oral administration of a construct comprising a nucleic acid molecule encoding a secreted protein antigen or an insulin protein, wherein said construct is encapsulated by a polymeric microcapsule, which is produced by phase inversion microencapsulation, said introducing resulting in introduction of the construct into an intestinal epithelial cell and secretion of the protein from the cell and into the bloodstream of the subject.

Mathiowitz *et al.* teach an identical method of orally delivering any mucosal epithelial surface,which includes the mucosal epithelial surface of the GI tract, of a DNA encoding an antigen or an insulin protein to a mammal, wherein the DNA is encapsulated in a polymeric capsule, *e.g.,* see claim 8 of the patent, columns 18-19. Column 20 discloses a number of agents that can be used to protect the DNA from degradation in the stomach. Columns 16 and 17 disclose that the DNA encodes an antigen or an insulin protein. Column 4 states that microcapsules are used interchangeably with microparticles and microspheres.

Note that the essential features of the claimed systems and/or compositions are that as long as a vector comprising a DNA of interest operably linked to a promoter is formulated in a composition suitable for *in vivo* administration, *e.g.,* a pharmaceutically acceptable carrier including a buffered solution, the non-viral vector would be able to function as intended, *e.g.,* delivery of any coding DNA and its subsequent expression and secretion into the bloodstream. The specification as a whole (pages 10-17, for example) clearly indicates:

> "Any nucleic acid vector having a eukaryotic promoter operably linked to a DNA of interest can be used in the invention to transform a secretory gland cell" (page 10, last paragraph); and
>
> "The DNA of interest can be any DNA sequence encoding any protein or other gene product" (page 18, first paragraph).

Absence evidence to the contrary, the protein encoded by the DNA construct of Mathiowitz is delivered the mucosal surface composed of epithelial intestinal cells, is expressed in the cells, and is released subsequently into the bloodstream of a treated mammal.

Applicant mainly argues that the functional limitation reciting a secretion and/or circulation of a protein produced by the claimed method comprising the same identical method materials and steps as employed in Mathiowizt does distinguish the claimed invention thereby putting all claims patentable (the response, page 13), The examiner respectfully submit that every method step and material employed in applicant's claimed invention is the same as that of Mathiowitz. As such and given the fact that applicant did not invent any novel construct and/or materials employed in the claimed methods, it would necessarily flows that the oral gene therapy method of Mathiowitz would result in a secretion and circulation of the expressed protein in the bloodstream. The examiner further notes that on one hand applicant argues that applicant's claimed invention, which claim broadly any oral gene therapy method comprising the use of any known non-viral vector including polymeric delivery vector encoding for any protein of interest, should be enabling under 35 USC 112, first paragraph, *e.g.,* successful delivery and subsequent expression of the protein in the bloodstream of any mammalian subject, on the other hand, applicant continues to argue that the very same method as described in Mathiowitz would not result in a successful delivery and subsequent expression of the protein in the bloodstream of any mammalian subject (the response, page 15). As such, the examiner notes that applicant 's response when read as a whole appears to be contradictory. Applicant further argues that the examiner inappropriately the theory of inherency, citing *Continental Can Co. USA, Inc. Monsanto, Motorola, Inc., v. Interdigital Technology Corp,* and *Ex parte Levy* (the response, page 13-15). In response the examiner maintains that applicant's response has been considered fully and is not found persuasive in view of the reasons set forth above, particularly since applicant has not been able provide any evidence that the very same construct when used in the very same administration step would not result in the natural delivery and of the expressed product into the bloodstream Further, Applicant appears to confuse that the limitation of "delivery into the bloodstream" is the same as an active step. The claimed invention coupled with as-filed specification does

not teach in any way of an active step of administering a construct into the bloodstream. Rather, the as-filed specification coupled with claims do indicate that as long as any non-viral vector encoding any protein of interest is employed in an active step of orally delivering the vector into a mammalian subject, the orally delivering construct at the site of the delivery (GI tract) would express the protein, and the protein would be naturally transferred by the endogenous pathways present in the GI tract into the bloodstream. As such and given that Mathiowitz teaches an oral gene therapy method of delivering actively to any mucosal epithelial surface, which includes the mucosal epithelial surface of the GI tract, of a DNA encoding an antigen or an insulin protein to a mammal, wherein the DNA is encapsulated in a polymeric capsule, the delivered DNA vector of Mathiowitz would have to necessarily express the antigen, which has to be subsequently and naturally transferred by the same endogenous pathways present in the GI tract into the bloodstream *in vivo*. As such and given the fact that identical active steps comprising the same materials are being claimed in an oral gene therapy described in the examined claims and the cited prior art, the functional limitation reciting the natural transfer of the expressed protein at the GI tract into the bloodstream *in vivo* must flow undeniably an d irrefutably from the expressed disclosure of the cited art of record.

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX

MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds*, may be reached at **(703) 305-4051.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 305-7401**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Primary Examiner

DAVE T. NGUYEN
PRIMARY EXAMINER